DETAILED ACTION

The present Office Action is responsive to the Amendment received on July 8, 2009.

Preliminary Remark

Claims 1-48 and 50-54 are canceled.

Specification

All objections to the specification made in the Office Action mailed on January 9, 2009 is withdrawn in view of the Amendment received on July 28, 2009.

Claim Interpretation

Applicants' election is drawn to a particular type of cancer, the cancer being colon cancer. The claims have been examined to the extent of their elected subject matter therefore.

Claim Rejections - 35 USC § 112

The rejection of claims 49 and 55-73 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on January 9, 2009 is withdrawn in view of the Amendment received on July 28, 2009.

The new matter rejection of claims 49 and 55-67 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, made in the Office Action mailed on January 9, 2009 is withdrawn in view of the Amendment received on July 28, 2009.

The rejection of claims 49, 55-70, and 73 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, made in the Office Action mailed on January 9, 2009 is withdrawn in view of the Amendment received on July 28, 2009.

Rejection, Maintained

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 49 and 55-73 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, made in the Office Action mailed on January 9, 2009 is maintained for the reasons already of record.

Applicant's arguments presented in the Amendment received on July 28, 2009 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments" section.

The Rejection:

The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation are summarized in In Re Wands (858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). They include (A) the quantity of experimentation necessary, (B) the amount of direction or guidance presented, (C) the presence or absence of working examples, (D) the nature of the invention, (E) the state of the prior art, (F) the relative skill of those in the art, (G) the predictability or unpredictability of the art, and (H) the breadth of the claims.

The Breadth of the Claims and & Enablement Issues:

The claims are broadly drawn to a method of diagnosing carcinoma or a propensity for carcinoma by comparing the expression of a nucleotide having 95%-99% sequence identity to SEQ ID NO: 869 in one sample with another sample from a normal tissue type.

The instant specification disclose that there are a number of viruses known to be involved in human cancer as well as in animal cancer and the ones of particular interest are viruses that do not contain oncogenes themselves, which induce tumors by integrating into the host genome and affecting neiboring protooncogenes in a variety of ways (section [0006]).

The instant specification discloses that with respect to lymphoma and leukemia, retroviruses such as AKV murine leukemia virus (MLV) or SL3-3 MLV, are potent inducers of tumors when inoculated into susceptible newborn mice, or when carried in the germ line and with respect to cancers, especially breast cancer, prost cancer and cancers with epithelial origin, the mammalian retrovirus, mouse mammary tumor virus (MMTV) is a potent inducer of tumors when inoculated into susceptible newborn mice, or when carried in the germ line.

The instant specification states that the instant invention is directed to a number of sequences associated with cancers, especially lymphoma, breast cancer or prostate cancer based on the "relatively tight linkage between clonally-integrated proviruses and protooncogenes" in that uninfected animals have low cancer rates, and infect animals have high cancer rates (section [0040]).

The specification states that the use of oncogenic retroviruses, whose sequences insert into the genome of a host organism resulting in cancer, allows the identification of host sequences involved in cancer. (section [0041]).

Based on this finding, the specification concludes:

"However, as it will be appreciated by those in the art, oncogenes that are identified in one type of cancer such as lymphoma or leukemia having a **strong likelihood of being involved in other types of cancers as well**." (section [0041])

The question of enablement is risen because the application has no data to support this general hypothesis that simply because there is a "strong likelihood" of an oncogene, which is involved in leukemia, being involved in other types of cancers, one of skill in the art would accept without question that any nucleic acid sequence involved in leukemia can be employed for diagnosis of other types of cancers, for the purpose of examination herein, colon cancer (the elected subject matter) and thus make and use the invention as claimed without undue experimentation.

Amount of Guidance:

The specification contains generalized description pertaining to detection of cancer, such as those employing hybridization detection (pages 46 and 56-64), immunoassays (pages 78-81).

The specification while disclosing that CA nucleic acids (whose list contains hundreds of SEQ ID Numbers, see Table 1 for example) can be downregulated or upregulated (in general), simply fails to disclose which of the nucleic acids are upregulated or downregulated for a particular cancer (for the present application, colon cancer).

In addition, the specification, simply has no data which would convey to one of skill in the art that the expression level of polynucleotide of SEQ ID NO: 869 or any of its homologs are implicated with colon cancer. There is simply guidance for the claimed invention other than general teachings of cancer diagnosis by nucleic acid hybridization which can be applied for any nucleic acids in general.

Working Examples:

There are no working examples for the method of diagnosing colon cancer by differential expression detection of cytochrome B5 or the polynucleotide of SEQ ID NO: 869 or its homologous sequences.

The state of prior art:

Those of skill in the art would also recognize that the diagnosis of cancer using specific biomarkers has many variables prior to any type of predictive success. Tockman et al. (Cancer Research, 1992, vol. 52, pages 2711-2718) teaches considerations necessary to bring a cancer biomarker to successful clinical applications. Prior to the successful application of newly described markers, research must validate the markers against acknowledged disease and end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective populations trials (Abstract). Early stage markers of cacinogenesis have clear biological plausibility as markers of preclinical cancer and if validated can be used for population screening (page 2713, 1st column). The artisans further express that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome.

Clearly, prior to successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (page 2716, 2nd column).

Lucentini et al. (The Scientist, 2004, vol. 18), share the importance of exercising cautions when implicating a biomarker with a particular disease, who titled his article, "Gene Association Studies Typically Wrong," and stating, "[t]wo recent studies found that typically, when finding is first published linking a given gene with a complex disease, there is only roughly a one-third chance that studies will reliably confirm the finding (page 2 of the print out).

This is consistent with the teachings of Wacholder et al. (Journal of National Cancer Institute, 2004, vol. 96, no. 6, pages 434-442) who notes that, "[t]oo many reports of association between genetic variants and common cancer sites and other ***complex diseases*** are false positives (see Abstract).

Skill Level & Unpredictability:

The instant invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). As Applicants' invention is derived from the hypothesis that cancers which are involved in leukemia have a strong likelihood of being involved in other cancers, such "germ of an idea," as the court expressed, is only a vague intimation that may or may not workable. Such "tossing out of" hypothesis would not constitute an enabling disclosure.

And as also set forth in *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297, 1302 (CAFC 2005), enablement cannot be established unless one skilled in the art "would accept without question" an Applicant's statements regarding an invention, particularly in the absence of evidence regarding the effect of a claimed invention. Specifically:

> "As we have explained, we have required a greater measure of proof, and for good reason. If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

Therefore, while the skill level of a skilled artisan is deemed high, as already discussed above, cancer is a highly complex disease involving a plurality of factors which are highly variable. Thus, based on the foregoing reasons, it is determined that one of skill in the art would not be able to practice the invention as claimed without undue experimentation.

Response to Arguments:

Applicants traverse the rejection.

Applicants state that "[e]nablement does not require absolute predictability" but rather, "requires that a person skilled in the art be able to practice the invention without undue experimentation." (page 13, 4th paragraph, Response)

Applicants state that no single factor is determinative, and that the enablement requirement is "met if a preponderance of the evidence indicates that it is **more likely than not that any person skilled in the art at the time the application was filed could have practiced the claimed method directed to diagnosing cancer or more specifically colon, breast, stomach or prostate cancer by comparing the expression of the recited cytochrome B5 encoding nucleic acids**..." (page 13, bottom paragraph to page 14, 1st paragraph, Response).

The examiner does not disagree with the Applicants in that no single element of the elements considered in *In re Wands* is always determinate of demonstrating enablement/non-enablement. The examiner also dose not disagree with the Applicants that enablement does not require absolute predictability, especially when it comes to methods pertaining to diagnosis as no single diagnosis is 100% accurate.

However, the point of disagreement between the Office and Applicants is in that it is the position of the Office that Applicants have not provided any disclosure to one of skill in the art that

cytochrome B5 is differentially expressed between cancerous and normal sample (in the present case, colon cancer), other than simple assertions made without any specific findings to support said assertions.

Applicants state that, "[a]s taught by the specification, the use of oncogenic retroviruses-whose sequences insert into the genome of the host organism and result in cancer – has allowed the identification of host cancer related sequences such as cytochrome B5" (page 14, 3rd paragraph, Response).

Applicants reference paragraphs, [0040], [0042], and [0062] for substantiating the above assertions (page 14, 3rd paragraph, Response).

Paragraphs [0040] and [0042] are disclose the general basis of using retroviruses for identifying host sequences involved in cancer, but does not substantiate or provide any factual evidence that cytochrome B5 is differentially expressed in cancer samples (i.e., colon cancer). In fact, paragraphs [0040] and [0042], while generally alleging their method as being useful for providing nucleic acid sequences which are associate with lymphoma/leukemia, breast or prostate, do not even contemplate colon cancer.

Section [0062] discloses the process by which CA sequences were identified. These sequences are disclosed as being identified by infection of mice with a retrovirus which resulted in lymphoma. This section asserts that when provirus form of the virus is inserted into the genomic DNA of the host cell, the provirus may affect the expression of host genes at or near the site of integration.

Initially, this section also generally alleges that the sequences identified by the above-discussed method, the specification does not provide any data with respect to the instantly claimed cytochrome B5 gene, and further with respect to its differential expression in colon cancer. As

Applicants are aware as known in the art, gene expression pattern for a marker observed for a particular cancer does not always follow the same patter for another cancer. In other words, a gene over-expressed in a particular type of cancer is not necessarily over-expressed in another type of cancer.

For example, Yang et al. (Biomedical Microdevices, 2005, vol. 7, no. 3, pages 247-251) in detecting common gene expression patterns in across multiple cancer types, clearly demonstrates that a particular gene determined for a particular cancer type is not necessarily indicative of another cancer (See Figure 1, where "LCP1" gene is down-regulated for leukemia only and non-significant for breast cancer).

What the specification fails to demonstrate is whether cytochrome B5 gene is observed as being consistently and significantly differentially expressed in at least the lung cancer samples.

In addition, what the specification fails to disclose is whether cytochrome B5 gene was differentially expressed in samples of individuals which was not retrovirus induced.

As previously stated in the rejection, those of skill in the art would also recognize that the diagnosis of cancer using specific biomarkers ***has many variables prior*** to any type of predictive success. Tockman et al. (Cancer Research, 1992, vol. 52, pages 2711-2718) teaches considerations necessary to bring a cancer biomarker to successful clinical applications. ***Prior to the successful application of newly described markers, research must validate the markers against acknowledged disease and end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective populations trials*** (Abstract). Early stage markers of cacinogenesis have clear biological plausibility as markers of preclinical cancer and if validated can be used for population screening (page 2713, 1st column).

The artisans further express that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome.

What is simply lacking from the instant application is whether the over-expression of cytochrome b5 gene was found in samples of individuals experiencing at least lung cancer and not from those whose cancer was produced by retroviral infection. In other words, the gene expression determined by the disclosed method is not a predictive model for determining whether such expression pattern is observed for individuals experiencing cancers via "natural" phenomenon without demonstration that such expression pattern was indeed observed consistently and significantly in a population of people/subjects experiencing lung cancer.

Applicants also refer to section [0062], [0064], and [0066] as well as [0175] for alleging support for the enablement of cytochrome B5 gene in lung cancer diagnostics (page 14, 3rd and 4th paragraph, Response).

Sections [0062], [0064], and [0066], are similar in disclosure to the other section of the specification to which Applicants point to, which only provide general allegation and description regarding CA (cancer associated) sequences, but not with respect to the claimed invention.

Section [0175] only discussed what is meant by the term, "differential expression" and has nothing to do with cytochrome B5 gene or its observed expression patterns in lung cancer samples.

Applicants also state that section [0284] through [0295] provide enabling teachings that the differential expression of cytochrome B5 or the cytochrome B5 encoding nucleic acids comprising SEQ ID NO: 869 can be used for diagnosing lung cancer (page 15, 1st paragraph, Response).

Section [0284] generally alleges that "alterations" found on the CA genes can be, "an indication of either the presence of the disease, or propensity to develop the disease, or prognosis evaluation." It is respectfully submitted that the instant application does not even disclose any

mutant forms (i.e., alterations found on the gene) of cytochrome B5 gene, let alone any correlation to their cancers.

Sections [0285]-[0295] are also drawn to general teachings regarding using gene fragments as probes for identifying the genes, or the labeling schemes for detection but have nothing to do with cytochrome B5 gene and its observed expression pattern in lung cancer samples.

Applicants contend that they have taught that cytochrome B5 gene encoding SEQ ID NO: 869, which was discovered through the retroviral insertional mutagenesis as a marker for diagnosis of cancer (page 15, bottom paragraph).

This argument also lacks evidentiary support in data.

There is simply no data for the Office to consider in determining whether cytochrome B5 gene was over-expressed in at least the lung cancer samples, consistently and significantly. The specification does not even provide from what cancer sample cytochrome B5 gene was determined to be over-expressed and how many samples were utilized in such a finding. As stated previously, a gene over-expressed in a particular type of cancer is not necessarily over-expressed in another type of cancer. Yang et al. (Biomedical Microdevices, 2005, vol. 7, no. 3, pages 247-251) in detecting common gene expression patterns in across multiple cancer types, clearly demonstrate that a particular gene determined for a particular cancer type is not necessarily indicative of another cancer (See Figure 1, where "LCP1" gene is down-regulated for leukemia only and non-significant for breast cancer).

In addition, what the specification fails to disclose is whether cytochrome B5 gene was differentially expressed in samples of individuals which were ***not*** retrovirus induced.

As previously stated in the rejection, those of skill in the art would also recognize that the diagnosis of cancer using specific biomarkers ***has many variables prior*** to any type of predictive

success. Tockman et al. (Cancer Research, 1992, vol. 52, pages 2711-2718) teaches considerations necessary to bring a cancer biomarker to successful clinical applications. ***Prior to the successful application of newly described markers, research must validate the markers against acknowledged disease and end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective populations trials*** (Abstract). Early stage markers of cacinogenesis have clear biological plausibility as markers of preclinical cancer and if validated can be used for population screening (page 2713, 1st column). The artisans further express that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome.

What is simply lacking from the instant application is whether the over-expression of cytochrome b5 gene was ***also*** found in samples of individuals experiencing at least lung cancer and not solely from those samples whose cancer was produced by retroviral infection. In other words, as currently disclosed, the gene expression determined by the disclosed method (i.e., mouse model) is not deemed a predictive model for determining whether such expression pattern is also observed for human individuals experiencing cancers via "natural" phenomenon.

> "A large number of the proto-oncogene and tumor suppressor loci found from retroviral screens have also been shown to be causally involved in human tumour development … ***This provides some validation for the use of these screens to model human oncogenesis***, and suggests that common insertion sites are useful candidates to **pursue** for mutation detection studies of ***human tumours***..." (Uren et al., Ocogene, 2005, vol. 24, pages 7656-7672, see page 7669, 2nd column, bottom paragraph)

As to the absence of the working examples found in the specification, Applicants state that MPEP 2164.02, does not require an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue experimentation (page 16, 4th and 5th paragraph, Response).

Applicants state that general teachings of RT-PCR used for analysis of differentially expressed genes, and the use of arrays can be demonstrative of enablement for the claimed invention.

As stated previously, it is respectfully submitted that general teachings known in the art cannot be demonstrative of the claimed subject matter. Can a general teaching regarding RT-PCR and the hybridization of said amplified products to microarray be demonstrative of any markers as being useful for any clinically known conditions without factual findings? Similarly, a general teaching regarding an overexpression of a gene marker cannot be an enabling disclosure of a different gene marker, when the specification fails to disclose any factual evidence.

It is noted that Applicants make reference to "Exhibit B" in their argument (see page 14, 3rd paragraph, Response). However, Applicants' response does not have any exhibit attached and thus cannot be considered. Applicants are invited to submit the exhibit in their response to the present office action should Applicants desire consideration of any factual finding/data. However, as stated previously, Applicants are reminded that findings determined from a mouse model are not necessarily predictive that the same findings will be found in human subjects.

Absent clear and convincing evidence (not simply pointing to general allegations made in the specification), the rejection will be maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the

mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 6:00 a.m. to 2:30 p.m (M-F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system,

see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Young J. Kim/
Primary Examiner
Art Unit 1637
10/28/2009

/YJK/